As a first matter, Applicants object to the prolonged and piecemeal prosecution of the present case. The Manual of Patent Examining Procedure provides that "[p]iecemeal examination should be avoided." M.P.E.P. §707.7(g). In the present case, the same rejections that are being raised by the Examiner in the present Office Action have been raised and obviated during earlier prosecution. Moreover, Applicants conducted an interview with the Examiner on May 9, 2002, during which the Examiner indicated that the currently pending claims would be allowable. Yet the Examiner has now issued an Office Action rejecting these same claims on the same grounds that were raised and overcome during earlier prosecution.

The Examiner's inconsistent and piecemeal examination of the present case is unfair to Applicants, contrary to United States Patent and Trademark Office practice and policy, and undermines the Examiner's rejections.

Objection to the Specification

The Examiner has objected to the amendment to the specification filed August 26, 2002 under 35 U.S.C. § 132, "because it introduces new matter into the disclosure." The Examiner further states that, "citations on the replacement sections filed August 26, 2002 are to references Published AFTER the filing date of the instant specification. This *a priori* constitutes new matter."

Applicants have no record of an amendment filed on August 26, 2002. However, a Preliminary Amendment was filed by Applicants on August 23, 2002 along with a Request for Continued Examination. In addressing this objection to the specification, Applicants assume that the Examiner is referring to the amendments made in the Preliminary Amendment of August 23, 2002.

Applicants respectfully submit that the references objected to by the Examiner are references on software programs that were inserted in the specification to replace hyperlinks that were objected to in a previous office action. In the present communication, Applicants have amended the specification by inserting references to the foregoing software programs that were published *prior* to the filing date of the instant application. These references were disclosed by

Applicants in the originally filed specification (see, for example, page 10, lines 18-19 of the originally filed specification), and thus do not constitute new matter. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing objection to the specification.

The Examiner has also objected to the specification because the ATCC accession number was not indicated.

Applicants respectfully submit that, pursuant to *In re Lundak*, Applicants have the right to make a deposit of a plasmid containing a nucleotide sequence encoding the NIP2b, NIP2cL, and NIP2cS molecules of the present invention, prior to issuance of the application. *In re Lundak* 723 F2.d 1216, 227 USPQ 90 (Fed Cir. 1985). Accordingly, Applicants reserve the right to amend the specification as originally filed to include the ATCC Deposit information for these molecules prior to issuance of the application.

Rejection of Claims 1,2, 4, 5, 8-12, and 29-41 Under 35 U.S.C. § 101

According to the Examiner, "[t]he rejection of claims 1-2, 4-5, 8-12, and 29-41 under 35 U.S.C. § 101is [w]ithdrawn based upon the amendment." However, the Examiner indicates that "[u]pon cancellation of the new matte[r], the rejection will be reinstated."

To begin with, Applicants respectfully submit that the amendments that the Examiner is referring to have no bearing on the utility of the present invention. As indicated above, the citations in the paragraph replacement sections filed on August 23, 2002 are references on software programs relating to the PFAM and HMM databases. These citations were used by Applicants to replace the hyperlinks to the PFAM and HMM databases objected to by the Examiner in a previous office action.

Even assuming *arguendo* that the amendments had a bearing on the utility of the present invention, which Applicants unequivocally dispute, Applicants have amended the specification to replace the citations that published *after* Applicants' filing date with citations that published *prior* to Applicants' filing date. As indicated above, these latter citations were part of the

originally filed patent application and, thus, do not constitute new matter. Thus, as no new matter is involved, Applicants respectfully submit that re-instatement of this 35 U.S.C. §101 rejection is not necessary.

Rejection of Claims 1,2, 4, 5, 8-12, and 29-41 Under 35 U.S.C. § 112

According to the Examiner, "[t]he rejection of claims 1-2, 4-5, 8-12[, and] 29-41 under 35 U.S.C. § 112 for failing to teach how to use the invention is withdrawn." However, the Examiner indicates that "upon cancellation of the new matte[r], the rejection will be reinstated." The Examiner states that, "the amendment to the specification is objected to because it introduces new subject matter into the specification. Specifically, a number of the cited references which are use[d] to lend support to the utility and description of the claimed invention were published subsequent to the filing date of this application."

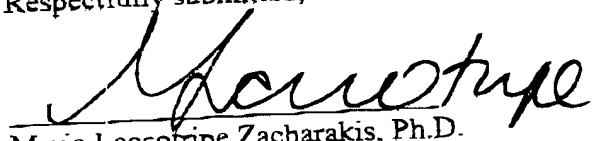
To begin with, Applicants respectfully submit that the amendments that the Examiner is referring to have no bearing on the utility of the present invention nor do they have any bearing on whether the pending claims satisfy the written description or enablement requirement of 35 U.S.C. §112, first paragraph. As indicated above, the citations in the paragraph replacement sections filed on August 23, 2002 are references on software programs relating to the PFAM and HMM databases. These citations were used by Applicants to replace the hyperlinks to the PFAM and HMM databases objected to by the Examiner in a previous office action.

Even assuming *arguendo* that the amendments had a bearing on the utility, enablement or "written description" of the present invention, which Applicants unequivocally dispute, Applicants have amended the specification to replace the citations that published *after* Applicants' filing date with citations that published *prior* to Applicants' filing date. As indicated above, these latter citations were part of the originally filed patent application and, thus, do not constitute new matter. Thus, as no new matter is involved, Applicants respectfully submit that re-instatement of this 35 U.S.C. §112 rejection is not necessary.

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,



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Limited Recognition Under 37 C.F.R. §10.9(b)

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Dated: February 19, 2003

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 10 lines 3-10:

--In another embodiment, a NIP2b, NIP2cL, and NIP2cS of the present invention is identified based on the presence of a "calcium-binding domain" in the protein or corresponding nucleic acid molecule. As used herein, the term "calcium-binding domain" includes a protein domain having an amino acid sequence of about 110 amino acids which has the capacity to bind calcium. Preferably, a calcium binding domain includes a protein domain which is at least 50, 60, 70, 80, 90, or 100 amino acid residues in length and which has the capacity to bind calcium The calcium-binding domain HMM has been assigned the PFAM Accession MILPAT0063 ~~(Bateman, A., *et al.* (2000) NAR 28: 263-266)~~ (Sonnhammer, *et al* (1997) *Proteins* 28:405-420).

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At page 10, lines 11-28:

--To identify the presence of a calcium-binding domain in a NIP2b, NIP2cL, or NIP2cS protein, and make the determination that a protein of interest has a particular profile, the amino acid sequence of the protein is searched against a database of HMMs (e.g., the Pfam database, release 2.1) using the default parameters ~~(Bateman, A., *et al.* (2000) NAR 28: 263-266)~~ (Sonnhammer, *et al.* (1997) *Proteins* 28:405-420). For example, the hmmsf program, which is available as part of the HMMER package of search programs, is a family specific default program for MILPAT0063 and a score of 15 is the default threshold score for determining a hit. Alternatively, the threshold score for determining a hit can be lowered (e.g., to 8 bits). A description of the Pfam database can be found in Sonhammer *et al* (1997) *Proteins* 28(3)405-420 and a detailed description of HMMs can be found, for example, in Gribskov *et al.*(1990) *Meth. Enzymol.* 183:146-159; Gribskov *et al.*(1987) *Proc. Natl. Acad. Sci USA* 84:4355-4358; Krogh *et al.*(1994) *J. Mol. Biol.* 235:1501-1531; and Stultz *et al.*(1993) *Protein Sci.* 2:305-314, the contents of which are incorporated herein by reference. A search was performed against the HMM database resulting in the identification of a calcium-binding domain in the amino acid

sequence of NIP2cL (SEQ ID NO: 5) at about residues 55-160 of SEQ ID NO:5 and NIP2cS (SEQ ID NO:8) at about residues 59-96 of SEQ ID NO:8. The results of the searches are set forth in Figures 8 and 9, respectively.--

At page 10, line 33 through page 11, line 11:

--In another embodiment, a NIP2b, NIP2cL, and NIP2cS of the present invention is identified based on the presence of a "4 transmembrane segment integral membrane protein domain" in the protein or corresponding nucleic acid molecule. As used herein, the term "4 transmembrane segment integral membrane protein domain" includes a protein domain having an amino acid sequence of about 50 amino acid residues and having a bit score for the alignment of the sequence to the "4 transmembrane segment integral membrane protein domain" (HMM) of at least 1 or greater. Preferably the term "4 transmembrane segment integral membrane protein domain" includes a protein domain having an amino acid sequence of about 60, 70, 80, or 90 amino acids and having a bit score for the alignment of the sequence to the "4 transmembrane segment integral membrane protein domain" (HMM) of at least 2, preferably 3-10, more preferably 10-30, more preferably 30-50, even more preferably 50-75, 75-100, 100-200 or greater. The "4 transmembrane segment integral membrane protein domain" HMM has been assigned the PFAM Accession PF00335 ~~(Bateman, A., *et al.* (2000) NAR 28: 263-266)~~ (Sonnhammer, *et al.* (1997) *Proteins* 28:405-420). A search was performed against the HMM database, as described herein, resulting in the identification of a "4 transmembrane segment integral membrane protein domain" in the amino acid sequence of NIP2b (SEQ ID NO:2) at about residues 253 to 293. The results of the search are set forth in Figure 7.--

APPENDIX A

1. An isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:1 or a complement thereof.

2. An isolated nucleic acid molecule comprising a nucleotide sequence which encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2, or a complement thereof.

4. An isolated nucleic acid molecule comprising a nucleotide sequence which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 2, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule consisting of SEQ ID NO:1 or 3 in 6X SSC at 45° C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65° C.

5. An isolated nucleic acid molecule comprising a nucleotide sequence which is at least 59% identical to the nucleotide sequence of SEQ ID NO:1, 3, 4, 6, 7, or 9, or a complement thereof.

8. An isolated nucleic acid molecule comprising the nucleic acid molecule of any one of claims 1, 2, 5, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, or 41 operatively linked to a nucleotide sequence encoding a heterologous polypeptide, wherein said isolated nucleic acid molecule encodes a fusion polypeptide.

9. A vector comprising the nucleic acid molecule of any one of claims 1, 2, 5, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, or 41.

10. The vector of claim 9, which is an expression vector.

11. A recombinant host cell comprising the nucleic acid molecule of any one of claims 1, 2, 5, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 40, or 41 operatively linked to a recombinant regulatory sequence.

12. A method of producing a polypeptide comprising culturing the host cell of claim 11 under suitable conditions to, thereby, produce the polypeptide.

27. An isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:3 or a complement thereof.

28. An isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:4 or a complement thereof.

29. An isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:6 or a complement thereof.

30. An isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:7 or a complement thereof.

31. An isolated nucleic acid molecule comprising the nucleotide sequence set forth in SEQ ID NO:9 or a complement thereof.

32. An isolated nucleic acid molecule comprising a nucleotide sequence which encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 5, or a complement thereof.

33. An isolated nucleic acid molecule comprising a nucleotide sequence which encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 8, or a complement thereof.

34. An isolated nucleic acid molecule comprising a nucleotide sequence which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:5, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule consisting of SEQ ID NO:4 or 6 in 6X SSC at 45° C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65° C.

35. An isolated nucleic acid molecule comprising a nucleotide sequence which encodes a naturally occurring allelic variant of a polypeptide comprising the amino acid sequence set forth in SEQ ID NO:8, wherein the nucleic acid molecule hybridizes to a nucleic acid molecule consisting of SEQ ID NO:7 or 9 in 6X SSC at 45° C, followed by one or more washes in 0.2X SSC, 0.1% SDS at 50-65° C.

36. An isolated nucleic acid molecule comprising a fragment of at least 461 nucleotides of a nucleic acid comprising the nucleotide sequence of SEQ ID NO:1, 3, 4, 6, 7, or 9, or a complement thereof.

37. An isolated nucleic acid molecule comprising a nucleotide sequence which encodes a polypeptide comprising an amino acid sequence at least about 60% identical to the amino acid sequence of SEQ ID NO:2, 5, or 8.

38. An isolated nucleic acid molecule comprising a nucleotide sequence which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, 5, or 8, wherein the fragment comprises at least 25 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:2, 5, or 8.

39. A method of expressing a polypeptide comprising the step of culturing the host cell of claim 11 under conditions in which the nucleic acid molecule is expressed, thereby expressing the polypeptide.

40. An isolated nucleic acid molecule comprising a nucleotide sequence which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, 5, or 8, wherein the fragment comprises at least 50 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:2, 5, or 8.

41. An isolated nucleic acid molecule comprising a nucleotide sequence which encodes a fragment of a polypeptide comprising the amino acid sequence of SEQ ID NO:2, 5, or 8, wherein the fragment comprises at least 100 contiguous amino acid residues of the amino acid sequence of SEQ ID NO:2, 5, or 8.